Recent insights into targeting the IL-6 cytokine family in inflammatory diseases and cancer

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Abstract

The interleukin-6 (IL-6) family of cytokines consists of IL-6, IL-11, IL-27, IL-31, oncostatin M (OSM), leukemia inhibitory factor (LIF), ciliary neurotrophic factor (CNTF), cardiotrophin-1 (CT-1), and cardiotrophin-like cytokine factor 1 (CLCF1). Membership of this cytokine family is defined by usage of common β-receptor signalling subunits, which activate various intracellular signalling pathways. Each IL-6 family member elicits responses essential to the physiological control of immune homeostasis, haematopoiesis, inflammation, development and metabolism. Accordingly, distortion of these cytokine activities often promotes chronic disease and cancer; the pathological significance of this is exemplified by the successful treatment of certain autoimmune conditions with drugs that target the IL-6 pathway. Here, we discuss the emerging roles for IL-6 family members in infection, chronic inflammation, autoimmunity and cancer, and review therapeutic strategies designed to manipulate these cytokines in disease.

[H1] Introduction

Cytokines contribute to all aspects of human biology and have evolved to enable the sensing and interpretation of environmental cues relevant to the maintenance of normal host physiology[1]. Although these secretory proteins are best known for their role as custodians of immune homeostasis and the inflammatory response to infection, trauma or injury, their diverse functions also affect embryonic development, cognitive function and behaviour, tissue integrity, and ageing. In this regard, cytokines often display pleiotropic or overlapping functional properties[1].

The interleukin-6 (IL-6) cytokine family comprises IL-6, IL-11, IL-27, IL-31, oncostatin M (OSM), leukemia inhibitory factor (LIF), ciliary neurotrophic factor (CNTF), cardiotrophin-1 (CT-1) and cardiotrophin-like cytokine factor 1 (CLCF1), and among all cytokine families it arguably displays the highest degree of functional pleiotropy and redundancy in eliciting responses relevant to health and disease[2]. Members of this family play prominent roles in chronic inflammation, autoimmunity, infectious disease and cancer (**BOX 1**), where they often act as diagnostic or prognostic indicators of disease activity and response to therapy[1,3-6]. Moreover, IL-6 family cytokines are now viewed as major therapeutic targets for clinical intervention[3-9]. This is epitomized by the treatment of chronic immune-related conditions, such as inflammatory arthritis, giant cell arteritis and Castleman's disease, with drugs that target IL-6[5,10-12]. In this Review, we will draw on recent advances to provide a timely update on the biology of IL-6 family cytokines and their clinical potential as therapeutic targets or disease modifiers in autoimmunity, inflammation, infection and cancer.

[H1] What constitutes IL-6 family membership?

IL-6 remains the archetypal member of the IL-6 cytokine family, and regulates a diverse array of functions relevant to haematopoiesis, tissue homeostasis, metabolism and immunity **(BOX 1 &**

BOX 2)[5,13]. Since the discovery of IL-6, subsequent investigations have revealed a high degree of functional redundancy amongst IL-6 family cytokines[14]. As a consequence, cytokines within this family are often described with activities attributed to lymphokines **[G]**, adipokines **[G]** or myokines **[G]**, which reflect their broad expression and cellular distribution among all major cell types within the body. This redundancy is characterized by a precise hierarchical involvement in inflammation, metabolism, development, tissue regeneration, neurogenesis and oncogenesis (**BOX 1 & BOX 2**)[15].

A defining feature of this cytokine family is its usage of common cytokine receptor subunits. These receptor complexes comprise the shared signal-transducing receptor β-subunit, glycoprotein 130kDa (gp130), together with either a ligand-binding non-signalling receptor α-subunit or a signalling receptor β-subunit that resembles gp130[2,15,16] (**FIG. 1**). The receptor signalling complexes for IL-6 and IL-11 contain a gp130 homodimer, whereas other family members signal via a heterodimeric receptor complex containing gp130 and an alternative signalling β-subunit (**FIG. 1**). The exception to this 'gp130 rule' is IL-31, which binds a cytokine receptor complex containing the OSM receptor β-subunit (OSMR) and a cognate IL-31-binding receptor termed cytokine-binding gp130-like protein (GPL, also known as IL-31RA)[17-19].

Phylogenetic analysis of cytokine families reveals that members of the IL-6 family share a close relationship with IL-12 family cytokines[20-22]. This link is illustrated by the heterodimeric composition of IL-27 (comprising IL-27p28 (also termed IL-30) and Epstein-Barr virus-induced protein-3; EBI3), which is structurally related to the IL-12 (IL-12p40–IL-12p35), IL-23 (IL-23p19–IL-12p40), IL-35 (IL-12p40–EBI3), and IL-39 (IL-23p19–EBI3) heterodimers[23-25]. Interestingly, both IL-27p28 and IL-35 can also signal via gp130[26,27], although the biological significance of this engagement with gp130 requires further substantiation, and thus their membership to the IL-6 family of cytokine is premature.

The functional diversity and redundancy associated with IL-6 family cytokines is partially explained by the presence of the ubiquitously expressed common gp130 signal-transducing receptor (**FIG. 1**). Use of the common gp130 receptor subunit contributes to the regulation of a wide range of overlapping activities that are controlled by IL-6 family cytokines. As a consequence, these cytokines play key roles in many physiological processes, including development, as evidenced by the embryonic lethality of gp130-deficient mice[28]. In contrast to gp130, the receptor subunits specific to individual family members display a more restricted cellular expression profile, and the phenotype of mice lacking individual cytokine family members or their associated receptor subunits is often less severe than their apparent pleiotropic properties would suggest[28,30,76,91].

While the tissue distribution of these receptors offers some distinction as to how individual family members act in defined cellular compartments, certain cytokines within the family have evolved several mechanisms that amplify or broaden their cellular activities. For example, human OSM can signal via gp130–LIFR or gp130–OSMR receptor complexes to mediate responses typically associated with LIF (for example, haematopoiesis)[17]. Receptor promiscuity can also elicit defined forms of cytokine receptor crosstalk. For instance, CNTF displays a low affinity interaction with IL-6Rα that can lead to the formation and activation of an IL-6Rα–gp130–LIFR signalling receptor complex[2,31]. Such cross-regulation may afford CNTF the capacity to control IL-6-related processes not normally associated with its primary involvement in the nervous system (for example, metabolism, bone remodelling, immune regulation) (**BOX 1 & BOX 2**)[32,33]. The complexities of IL-6Rα usage also extend to cytokines beyond the IL-6 cytokine family, with a recent example being IL-27p28, which moderates inflammatory activities through engagement of an IL-6Rα–gp130 receptor system[27,34,35].

In addition to these ‘classical’ mechanisms of cytokine receptor signalling, several members of the IL-6 family employ alternative modes of gp130 activation termed ‘cytokine

trans-signalling' (relevant to IL-6, IL-11, CNTF) and 'trans-presentation' (relevant to IL-6) (**BOX 3**). These alternative modes of cytokine signalling are best epitomized by the action of IL-6, and we refer the reader to several recent articles that review the regulation and biological properties of classical IL-6 receptor signalling and IL-6 trans-signalling in health and disease[5,15,17,29,36-38]. Briefly, classical IL-6 receptor signalling describes activities mediated via the membrane-bound IL-6 receptor complex, and is restricted to cells that express both IL-6Rα and gp130[29]. In contrast, IL-6 trans-signalling denotes a process that involves IL-6 binding to a soluble form of IL-6Rα (sIL-6R), which maintains the circulating half-life of IL-6, and enhances its bioavailability[39,40]. Interestingly, sIL-6R shares sequence identity with both IL-12p40 and EBI3, and once bound with IL-6 resembles a heterodimeric cytokine similar to IL-12-related cytokines[5,20,41]. In this regard, the IL-6:sIL-6R complex is able to directly engage and activate membrane-bound gp130 to facilitate IL-6 signalling in cell types that would not normally respond to IL-6[29]. Thus, trans-signalling serves to broaden the target cell repertoire of IL-6, and is considered the primary mechanism for IL-6 involvement in numerous chronic diseases and cancers[5,29,37]. Intriguingly, similar cytokine trans-signalling mechanisms have been described for IL-11 and CNTF, and recent *in vitro* observations infer that both IL-27p28 and EBI3 can also induce sIL-6R-mediated forms of trans-signalling (**BOX 3**)[2,15,35,42-44]. While the *in vivo* consequences of these latter signalling modes require further evaluation, the identification of soluble variants of gp130 (sgp130) in human serum, urine and inflammatory exudates that antagonize both IL-6 and IL-11 trans-signalling emphasizes the biological significance of these alternative signalling mechanisms[17,29,38,44].

[H1] Regulation of intracellular signalling

All IL-6-related cytokine receptor complexes transduce intracellular signals via the Janus kinase (JAK) – signal transducer and activator of transcription (STAT) pathway **[G]**, where receptor-

associated JAKs (namely, JAK1, JAK2 and TYK2) activate the latent transcription factors STAT1, STAT3 and (to a lesser extent) STAT5 (**BOX 1**)[6,9,16]. Other signalling intermediates activated in response to IL-6 family cytokines include: first, the protein tyrosine phosphatase SHP2 (also known as PTPN11), which promotes activation of the RAS–RAF–extracellular signal-regulated kinase 1 (ERK1)/ERK2 mitogen-activated protein kinase *(*MAPK) and phosphotidylinositol-3-kinase (PI3K)–protein kinase B (PKB, also known as AKT) pathways; and second, the transcription factor CAAT-enhancer binding protein β (C/EBPβ, also known as NF-IL-6) (**BOX 1**)[16]. Recently, IL-6- and IL-11-induced activation of PI3K was shown to regulate the mTOR complex 1 (mTORC1) system, which controls telomerase activity and protein synthesis, and influences various cellular processes including metabolism and redox stress (**BOX 1**)[45,46]. The diverse signalling networks activated by IL-6 also extend to Notch and Yes-associated protein (YAP), which upon gp130–SRC kinase-dependent activation facilitate epithelial cell proliferation and tissue remodelling or regeneration (**BOX 1**)[47].

The pathophysiological consequences of dysregulated gp130 activation on immune homeostasis and susceptibility to infection, autoimmunity or cancer have been widely reported, thus highlighting the importance of restricting the magnitude or duration of IL-6 cytokine family signalling in disease[48-52]. In this respect, multiple negative-regulatory mechanisms have evolved to curtail gp130-dependent signalling. These include receptor internalization, deactivation of receptors and signalling intermediates by protein tyrosine phosphatases, microRNA (miR)-mediated translational repression and degradation of target mRNAs encoding cytokines or their receptors, and the STAT-driven induction of protein inhibitors of activated STAT (PIAS) and suppressor of cytokine signalling (SOCS) factors[9,16,53,54]. Among these, SOCS3 plays the predominant negative regulatory role via inhibition of JAK-STAT3 activation, and targeting cytokine receptor complexes for proteasome degradation[53].

Considering the global cellular processes activated by the above signalling cascades, it is not surprising that IL-6 family cytokines display widespread functional pleiotropy (**BOX 1**). So, how do individual family members acquire unique biological specificity? Early investigations of STAT factors and their interaction with the genome provided evidence of cooperative mechanisms with other transcription factors, competition for overlapping transcription factor binding sites in gene promoter regions, and interaction with other transcriptional co-activators or co-repressors[9,53,55]. For example, the STAT3-mediated transcriptional output of IL-6 family cytokines can be influenced by the interaction of STAT3 with co-activators (such as p300–CBP) and other transcription factors, including nuclear factor-κB (NF-κB). NF-κB complexes with STAT3 in an unphosphorylated state to drive a distinct transcriptional signature enriched for genes involved in oncogenic and immune responses[56-59]. Interestingly, there is also an alternative mode of transcriptional control employed by STAT3. This occurs downstream of IL-6 and IL-11 and involves the induction of specific miRs implicated in tumourigenesis and epithelial–mesenchymal transition (for example, miR-21 and miR-200 family members)[60,61].

Another mechanism by which individual IL-6 family members achieve biological specificity involves cross-regulation between individual STAT proteins[9,62-65]. For example, in cells lacking STAT1, STAT1-activating cytokines (for instance IFNγ) show enhanced STAT3-type responses, such as increased cell survival, proliferation and induction of immune tolerance. Conversely, in STAT3-deficient cells, IL-6 induces STAT1-associated cellular effects, such as inhibition of cell proliferation, induction of apoptosis and promotion of anti-tumour immunity[9,63,65]. Notably, a series of studies investigating the differential transcriptional responsiveness of T cells to IL-6 and IL-27 has uncovered novel insights into how cross-regulation between STAT1, STAT3 and STAT5 can determine the effector characteristics of $CD4^+$ T helper cells[9,66,67]. Specifically, while both cytokines transcriptionally regulate a comparable number of genes, a small number of immunoregulatory genes were differentially expressed (for example, *Ifng*, *Ccl5* and *Rorc*), which

reflect the opposing pro-inflammatory and immunosuppressive functions assigned to IL-6 and IL-27[67]. In this setting, STAT3 provided the bulk of the overall transcriptional responsiveness to each cytokine, while STAT1 shaped the transcriptional programme specific to either IL-6 or IL-27.

[H1] Critical modulators of innate immunity

During inflammation, IL-6 family cytokines regulate innate immunity through direct effects on innate immune cells, and indirectly via activation of stromal tissue cells resident to the site of inflammation (**BOX 1**). These activities influence changes in leukocyte recruitment, their functional activation, differentiation and survival, and the development of a more sustained adaptive immune response[5,15,17,68]. Importantly, such roles illustrate why therapeutic targeting of IL-6 family members has been often associated with clinical benefit in inflammatory diseases, where these processes are distorted or skewed.

The capacity of IL-6 family cytokines to regulate almost every aspect of the innate immune system is facilitated, at least in part, by their signalling interplay with the complement system and pattern recognition receptors **[G]**[69,70]. For example, IL-6 receptor, complement component C5a receptor and Toll-like receptor 4 (TLR4) signalling share a complex interaction that is relevant to the control of bacteraemia and sepsis[71-73]. Such interactions may include the collaborative crosstalk that exists between STAT3 and NF-κB[74,75]. Thus, IL-6 and other IL-6-related cytokines often work in association with innate sensing systems to link innate and adaptive immunity, and to control anti-microbial defense.

Studies on IL-6, IL-27, OSM and LIF highlight important roles for these cytokines in anti-microbial and anti-viral immunity, where they provide tissue protection from infection-related injury[68,71,76-79]. These cytokines often control the recruitment, adhesion, survival and effector activities of neutrophils, tissue-resident and inflammatory monocytes, and innate lymphoid cell

populations (for example, natural killer (NK) cells). Specifically, these activities include the regulation of neutrophil-activating chemokines (for example, CXC-chemokine ligand 1 (CXCL1), CXCL5, CXCL6 and CXCL8), adhesion molecules (for example, intracellular adhesion molecule 1 (ICAM1), vascular cell adhesion molecule 1 (VCAM1) and L-selectin) and apoptotic regulators (for example, B cell lymphoma 2 (BCL-2) and BCL-XL)[37,80]. In this regard, several *in vivo* studies have shown that IL-6 family cytokines affect the accumulation of specific immune cell subsets within inflamed tissues[81-84]. For instance, IL-6 deficiency leads to prolonged neutrophil infiltration at sites of infection[85]. Neutrophil function is, however, impaired in *Il6*$^{-/-}$ mice infected with *Candida albicans*, which may account for the loss of infection control and enhanced dissemination of the pathogen in these mice[86]. Interestingly, these activities are not directly governed by IL-6 acting on the neutrophil infiltrate. Instead, neutrophil phagocytosis and killing is controlled by inflammatory mediators released by stromal tissue cells, such as endothelial, smooth muscle, epithelial and mesothelial cells and fibroblasts, in response to IL-6 trans-signalling[37]. In this scenario, the local regulation of IL-6 trans-signalling is reliant on the initial neutrophil infiltrate, which secretes sIL-6R within the inflamed tissue as a response to specific stimuli (for example, C-reactive protein, inflammatory chemokines, complement components, bioactive lipids, N-formyl peptides)[5,37]. Thus, sIL-6R is an alarmin that affects innate and adaptive immune outcomes[29,37]. The importance of this form of IL-6 regulation is exemplified by individuals carrying a specific *IL6R* polymorphic mutation (rs2228145)[5,29,87,88]. These individuals display heightened levels of circulating sIL-6R and this is associated with reduced markers of systemic inflammation and lower risk of coronary heart disease[89,90]. While these findings appear counterintuitive given the proposed importance of IL-6 trans-signalling in chronic and autoimmune disease, one must consider the wider properties of a soluble cytokine receptor[17,29,38]. These include maintaining the circulating half-life of the cytokine. In this context, the heightened sIL-6R levels complex with IL-6 and increase the bioavailability of the IL-6–sIL-6R

complex for antagonism by sgp130 to impair IL-6 signalling capacity[17,29,38].

What of the other IL-6-related cytokines? While the phenotypic characteristics of mice lacking IL-6, IL-11, LIF or CNTF reveal a degree of functional redundancy[28,30,76,91], individual cytokines sit within a defined hierarchy. For example, in models of autoimmunity (such as inflammatory arthritis), *Il6*$^{-/-}$ and *Il6ra*$^{-/-}$ mice are protected, whereas *Il11ra*$^{-/-}$ and *Osmrb*$^{-/-}$ mice develop a disease severity comparable to wild-type mice[92]. Instead, *Il11ra*$^{-/-}$ and *Osmrb*$^{-/-}$ mice display other aspects of pathology, including impaired hepatocyte proliferation, altered bone turnover and monocytic cell trafficking, thymic hyperplasia and glomerulonephritis[93-96]. These studies illustrate the involvement of IL-6-related cytokines in immune homeostasis and innate immune activation, and emphasize the context-dependent nature of their activities. Understanding these subtle differences and their biology is essential when considering the design or clinical application of therapeutic interventions that target members of the IL-6-related family.

[H1] Orchestrators of adaptive immunity

The regulatory capacity of IL-6-related cytokines in adaptive immunity is defined by their effects on the maturation of B cells into antibody-secreting cells, the survival and maintenance of long-lived plasma cells, and the generation of lymphocytes with defined phenotypic or effector characteristics. While these activities often rely on the prior activation of innate immune responses in monocytes and specialized antigen-presenting cells, several IL-6 family cytokines (for example, IL-6 and IL-27) also act as lymphokines of adaptive immunity (**BOX 1**). For instance, IL-6 controls the effector characteristics of various CD4^{+} T helper (Th) cell populations, with initial investigations showed that IL-27 instructs Th1 cell development and promotes expression of IFNγ, the Th1 cell transcriptional regulator T-bet, STAT1 and IL-12Rβ2[5,23,68,97]. The role of IL-27 has since been broadened to include negative regulation of IL-2 signalling and restricting the

development of immune responses through the expansion of T-bet^{+}CXCR3^{+} regulatory T (Treg) cell populations in Th1-cell mediated models of inflammation (such as acute *Listeria monocytogenes* infection)[98-104]. Thus, IL-27 is often protective in mouse models of chronic infection (for example, leishmaniasis and toxoplasmosis) and autoimmunity (for example, inflammatory arthritis, chronic inflammation of the central nervous system), and *Il27ra*$^{-/-}$ mice typically develop heightened or adverse T cell-mediated disease[23,68]. In contrast, IL-6 drives tissue-specific pathology and fibrosis through the expansion of IFNγ-secreting Th1 cells[105]. Interestingly, IL-6 does not directly promote the differentiation of Th1 or Th2 cells from naive CD4^{+} T cells, but instead controls the survival of these cells by supporting the action of other lymphokines[5]. Moreover, IL-6 acts as a cytokine commitment signal for the expansion of effector T cell populations, including Th17 and Th22 cells[5]. Regarding the former, IL-6 together with IL-1β, transforming growth factor β (TGFβ), IL-21 and IL-23 controls the expression of Th17 cell-associated gene signatures (for example, genes encoding IL-17A, IL-17F, IL-22, RORγt and the aryl hydrocarbon receptor; AhR)[5]. Th17 cells play vital roles in maintaining mucosal barrier integrity and immunity, protection against fungal infections, and in the development of inflammation-associated tissue damage, and may reflect the contribution of IL-6 in maintaining tissue integrity and immune homeostasis at barrier surfaces[106-108]. Conversely, IL-27 acts as a negative regulator of certain effector characteristics and inhibits the generation of Th17 cells through the actions of STAT1[68,103,109]. A similar interaction may also apply to IL-11 and OSM, which have been reported to drive or inhibit Th17 development, respectively[110,111]. However, it is unclear whether these alternative roles of IL-11 and OSM control the expansion of Th17 cell populations in draining lymph nodes or affect the maintenance of pathogenic effector T cells in inflamed tissues.

As discussed earlier, the contrasting lymphokine properties of IL-6 and IL-27 are primarily controlled by subtleties in the regulation of STAT1 and STAT3[112]. Among IL-6 family cytokines,

only IL-27 preferentially activates STAT1, and this IL-27–STAT1 axis often inhibits the IL-6-mediated control of STAT3 to alter the effector or regulatory characteristics of T cell subsets[97]. This is exemplified by the ability of IL-27 to block the commitment towards Th17 cells through STAT1 control of STAT3 signalling[67,113-116]. This inhibitory signal is lost in STAT1-deficient T-cells, where IL-27 switches to promote expansion of Th17 cell populations via STAT3[67,113]. Thus, alterations in the balance of cytokine-driven STAT1 and STAT3 signalling may yield distinct biological outcomes, which will shape the pattern of adaptive immunity controlled by IL-6-related cytokines. For example, while IL-6 inhibits Treg cell function and prevents the conversion of Th17 cells into Treg cells, IL-27 stimulates suppressive Treg cell activities that regulate the expression of cytotoxic T lymphocyte antigen 4 (CTLA4) and programmed cell death protein 1 (PD1)[117-121]. The challenge now is to understand how IL-6-related cytokines influence the pathogenesis and clinical management of disease through activation of these immunological outcomes.

[H1] Determinants of chronic autoimmune diseases

With impacts on stromal tissue cells, tissue-resident monocytes and activated inflammatory leukocytes, IL-6 family cytokines play vital roles in the initiation, maintenance and resolution of local and systemic inflammatory outcomes that promote tissue damage, activation of the acute phase response, development of autoimmune reactions, and metabolism (**BOX 1 & BOX 2**)[5,15,17,122-126,]. As a consequence, IL-6 family cytokines play a central role in the progression of chronic disease and autoimmunity (**BOX 1**).

Early investigations revealed that *Il6*$^{-/-}$ mice display various immunological defects, including impaired humoral immunity (for example, mucosal IgA antibody responses), an inability to mount an effective anti-microbial host defense against bacterial, fungal and viral infections, and a reduced capacity for wound healing[76,127,128]. In experimental models of

autoimmune or inflammatory diseases, including inflammatory arthritis, multiple sclerosis, renal injury and scarring, multicentric Castlemans's disease and plasmacytoma, *Il6*$^{-/-}$ mice display a highly protective phenotype, and show limited histological evidence of pathology[5,129]. The administration of blocking anti-IL-6 or anti-IL-6R antibodies, or sgp130 to wild-type mice often recapitulates these findings, and has supported the development of biological drugs against IL-6[5,15,29].

At sites of disease, members of the IL-6 cytokine family drive inflammation-induced tissue damage. These activities are highly context-dependent, but invariably distort the physiological turnover of extracellular matrix and tissue remodelling. This is particularly evident in episodes of fibrosis, where IL-6, IL-11, IL-31 and OSM contribute to fibrotic lesions in the liver, lung, heart, skin, kidney and peritoneal cavity[81,105,130-134]. The development of these fibrotic events typically involves a loss of immune homeostasis and the physiological maintenance of tissue integrity. In particular, fibrosis and scarring often arise from an altered expression of matrix metalloproteases and tissue inhibitors of matrix metalloproteases, and the regulation of angiogenesis and vasculopathy. Several of these outcomes involve partnerships with other pro-fibrotic cytokines (for example, IL-4, IL-13, TGFβ, CNTF and IFNγ), and the expansion of effector CD4^{+} T cell populations that shape inflammatory activities within the stromal tissue compartment[81,105,133,135-138]. Such alterations in tissue architecture invariably lead to loss of tissue or organ function. For example, elevated levels of IL-6 in the urine of patients with acute kidney injury or mesangial proliferative glomerulonephritis is often associated with poor clinical outcomes[139,140]. These observations reflect findings from animal models where IL-6 drives renal inflammation, tissue damage, and increased proteinuria[87]. However, the role of IL-6 in kidney disease may also relate to a breakdown in the homeostatic contribution of IL-6 to normal kidney function. For example, in tubular epithelial cells, IL-6 acts to preserve renal function and prevent damage of the epithelial lining[141]. Similar scenarios are also seen in the lung and gut where IL-6

(via trans-signalling) juggles the balance between homeostatic control of epithelial function and barrier integrity, and the onset of pulmonary airway or colitis-like inflammation[47,142,143].

In inflammatory or degenerative forms of arthritis, members of the IL-6 cytokine family promote synovial hyperplasia, maintenance of joint inflammation, and damage to the underlying cartilage and bone. These hallmarks of disease are primarily regulated by STAT3, whose activity is largely confined to the synovial lining and clusters of $CD3^+$ T cells within the inflamed synovium[7,144-147]. For example, gp130 knock-in mice, which display exaggerated JAK–STAT signalling, show worse joint pathology and heightened synovial inflammation in a model of arthritis[114,147,148,]. Indeed, a monoallelic deletion of *Stat3* in these mice reduces the recruitment and retention of inflammatory leukocytes, improves joint pathology and decreases disease activity[147-150]. In this regard, IL-6, IL-11, IL-27, OSM and LIF have significant effects on both cartilage and bone erosion via their regulatory actions on bone turnover and RANKL-mediated osteoclastogenesis[151-156]. Clinical correlates and experimental studies emphasize that IL-6 trans-signalling coordinates many of these outcomes and is an important determinant of leukocyte infiltration and the severity of joint destruction[33,147,157-161]. Consequently, IL-6 trans-signalling is now considered the main protagonist of local IL-6-driven pathology, and therapeutic targeting of this mode of IL-6 signalling in animal models of inflammatory disease frequently leads to improved disease outcomes[5,29].

While STAT3 activation by IL-6 family cytokines promotes disease processes, the contribution of cytokine signalling through STAT1 often appears to dampen disease activity[3,29,162-166]. This is illustrated by studies in *Il27ra*$^{-/-}$ mice, which display severe tissue pathology in models of infection and autoimmunity[97,167]. Although some of these effects relate to the impact of IL-27 on effector T cell populations, IL-27 also directs various tissue-specific responses in antigen-presenting cells, innate immune cells and B cells, as well as other stromal cells[68,97,167]. One interesting feature of the tissue pathology seen in *Il27ra*$^{-/-}$ mice is the

development of ectopic lymphoid-like structures (ELS) at sites of inflammation. These organized lymphoid aggregates are often seen in infection, autoimmunity and cancer, and their presence determines clinical outcome or response to therapy[168]. In synovial biopsies from rheumatoid arthritis patients with early or established disease, inverse correlations exist between IL-27p28 and the development of highly organized lymphoid-rich aggregates and autoantibody production[169]. Patients with this form of lymphoid-rich synovitis typically display severe or rapidly progressing disease and show poor response to standard biological drugs[168,170]. Consistent with IL-27 being a negative regulator of ectopic lymphoneogenesis, this inverse relationship is also evident in *Il27ra*$^{-/-}$ mice where the experimental onset of inflammatory arthritis is associated with elevated synovial expression of various mediators implicated in lymphoid neogenesis, including homeostatic chemokines (for example, CXCL13, CC_chemokine ligand 21 (CCL21) and CCL19), pro-inflammatory cytokines (for example, IL-17 and IL-21), follicular dendritic cell markers (for example, CD21) and transcriptional regulators (for example, BCL-6)[169]. Although the precise mechanism of ELS inhibition by IL-27 requires further investigation, these clinical and experimental studies suggest a role for T follicular helper (Tfh) cells or specialized Th17 cells, the latter of which can promote ELS formation in inflamed tissues from mice with pulmonary inflammation or experimental autoimmune encephalomyelitis[171,172]. Indeed, several of the genes associated with ectopic lymphoneogenesis are regulated by STAT3 (for example, *IL21*, *CXCL13*, *Bcl6*), and the action of IL-27 in this setting may influence the transcriptional control of Th17-like and Tfh-like cells by inflammatory cytokines such as IL-6 and IL-21[173].

In summary, IL-6-related cytokines play crucial roles in the orchestration of inflammatory processes relevant to the initiation, progression and diversity of disease activities seen in autoimmune and inflammatory diseases (**BOX 1**). As discussed in the next section, many of these responses are relevant to cancer, and influence both the pattern of tumour-associated

inflammation and the proliferative expansion or tissue invasion of cancerous cells.

[H1] Contrasting roles in cancer

Dysregulated IL-6 family cytokine expression or downstream receptor signalling are frequent events in cancer and are often associated with poor clinical outcomes[4,174-177]. In this regard, the pro-tumourigenic actions of IL-6 cytokine family members are elicited by both direct intrinsic effects on cancer cell activities (for example, cell proliferation, survival, migration, invasion and metastasis), and indirect effects on the stromal cell compartment, such as modulation of inflammation, immunosuppression and angiogenesis, which shape the local tumour microenvironment **[G]** (**FIG. 2**)[4,174-178]. Furthermore, the link between these cytokines and cancer extends to the recent evidence that some family members (for example, IL-6) are important regulators of energy metabolism (**BOX 2**), which is considered a hallmark feature of the initiation and progression of tumour growth[122,123,126]. Paradoxically, accumulating evidence suggests that some IL-6 family cytokines can also mount anti-tumour responses. The challenge, therefore, is to discern how the dynamic interplay between pro- and anti-tumourigenic activities arises in different tissue compartments, and how this interplay influences responses to biological drugs or immunotherapies that modulate cytokine activity.

[H2] Tumour cell-intrinsic effects. Interleukin-6 is the prototypical pro-tumourigenic cytokine within the IL-6 cytokine family and regulates various STAT3-mediated oncogenic processes (**FIG. 2**)[6,50,69,176]. For example, IL-6 potentiates the transcriptional induction of numerous molecular targets essential for cell cycle progression and survival (for example, cyclin D1, MYC, BCL-XL, survivin, miR-21), angiogenesis, and tumour invasion and metastasis (for example, hypoxia-inducible factor 1α (HIF-1α), matrix metalloproteinase 2 (MMP-2), MMP-7, MMP-9, vascular endothelial growth factor (VEGF))[60,61,149,174]. Thus, IL-6 contributes to both the initiation and

rapid progression of tumourigenesis. In late stage disease, IL-6 also propagates the metastatic spread of invasive cancer cells by inducing transcriptional activators of epithelial–mesenchymal transition (EMT), such as SNAIL and TWIST[179]. Importantly, the growth-potentiating effects of IL-6 on cancer cells also extend to cancer stem cells, whose self-renewal and population expansion requires STAT3 in concert with stem cell transcription factors such as NANOG[180]. These interactions ultimately contribute to the progression of several multidrug resistant epithelial and haematologic malignancies[180].

Interleukin-11, LIF and OSM also display cancer-cell-autonomous pro-tumourigenic activities, many of which overlap with IL-6. For example, in cancers of the gastrointestinal tract and breast, IL-11 directly fuels tumour growth by inducing STAT3-regulated gene and miR networks that promote cell cycle progression, anti-apoptotic activities and angiogenesis[4,177,178,181]. In gastric cancer, the IL-11–STAT3 axis can promote expression of a TLR2 innate sensing mechanism essential for gastric tumour cell proliferation and survival[177]. In addition, IL-11, LIF and OSM utilize JAK–STAT3 and PI3K–AKT–mTOR pathways to promote EMT-associated cancer cell invasion and metastasis (including that of bone), and the self-renewal and expansion of cancer stem cell populations[182-185]. Indeed, the activation of these pathways by OSM and LIF often propagates resistance to targeted therapies and is relevant to both breast and lung cancer[186,187]. Although the cancer cell-intrinsic actions of CLCF1, CNTF, CT-1, IL-27 and IL-31 family members are less defined, emerging evidence suggests that IL-31 maybe pro-tumourigenic in some lymphomas[18].

Despite the use of shared receptor signalling pathways, some cytokines within the IL-6 family display opposing anti-tumour effects on cancer cells. For instance, in a PTEN-deficient prostate cancer model, IL-6–STAT3 signalling in tumour cells protects against tumour progression by maintaining an intact senescence-inducing ARF–MDM2–p53 tumour suppressor axis[188]. The anti-tumour effects of this family are also illustrated by comparing the properties of

IL-27 and OSM in various epithelial and haematological malignancies. Here, a regulatory interplay exists between STAT1 and STAT3, whereby IL-27 and OSM (via STAT1) counteract various STAT3-driven processes linked with tumour cell survival, proliferation, metastatic invasion and angiogenesis[189,190]. This differential switch in shared signalling pathways provides an attractive molecular explanation for the opposing pro- and anti-tumourigenic activities of the broader IL-6 cytokine family. More investigations are required, however, to establish how the balance of STAT1 and STAT3 signalling shapes the transcriptional landscape in different stages of neoplastic progression, and within the tumour microenvironment.

[H2] Tumour cell-extrinsic effects. The tumour microenvironment of most cancers is immune cell-rich and immunosuppressive, and often under the influence of the complex immunomodulatory actions of the IL-6 family cytokines. The nature of this milieu has placed a heavy emphasis on research that aims to understand how these cytokines influence cancer inflammation and tissue remodelling in and around the tumour site, as well as the access and bioactivities of anti-cancer immunotherapies. Among IL-6 family cytokines, IL-6 elicits the most defined impact on the tumour microenvironment by promoting chronic inflammation that supports tumour angiogenesis and the outgrowth of transformed cells, whilst suppressing Th1 cell-mediated anti-tumour immunity (**FIG. 2**)[191]. These pro-tumourigenic activities impact on the recruitment, retention and activity of tumour-infiltrating leukocytes, and are equally diverse as the pleiotropic innate and adaptive immune responses mediated by IL-6 in autoimmune and chronic inflammatory diseases. Specifically, the pro-tumourigenic effects of IL-6 include the generation of pathogenic Th17 cells and myeloid-derived suppressor cells (MDSCs), the suppression of antigen-presenting dendritic cells and anti-tumour cytotoxic $CD8^+$ T cells and Treg cell activity, and the phenotypic switching of tumour-associated macrophages from a tumouricidal 'M1-type' phenotype to an immunosuppressive 'M2-type' macrophage

phenotype[191]. While further research is required in this area, we expect that other members of the IL-6 cytokine family may elicit similar outcomes. For example, IL-11 promotes inflammation-associated tumourigenesis in the gastrointestinal tract and shares the capacity with IL-6 to polarize T cells and macrophages towards a more immunosuppressive phenotype[4,178,181,192].

In addition to its effects on tumour-associated immune cells, the activities of IL-6 on cancer-associated fibroblasts and adipocytes have attracted considerable interest for their indirect tumour-promoting effects. Since the interplay between IL-6 and fibroblasts in cancer has been covered elsewhere[193], we will summarize here the recent evidence for IL-6 being an adipocyte-secreted cytokine ('adipokine') with the potential to modulate interactions between inflammatory and metabolic processes intrinsic to carcinogenesis. This idea is extremely relevant, given the increased risk of cancer in obese individuals with metabolic disorders, which are associated with heightened systemic inflammation. The activities of IL-6 as an adipokine, however, have been largely explored in the context of the paraneoplastic syndrome of cachexia **[G]**, typified by wasting of adipose and muscle tissue[125]. For example, in murine models of lung and pancreatic cancer-associated cachexia, IL-6 promotes an increase in the proportion of brown fat within inflamed adipose tissue. These changes lead to enhanced mitochondrial activity and associated systemic metabolic responses that increase energy expenditure and wasting[125]. Furthermore, the intricate interplay between IL-6-mediated suppression of tumour immunity and dysregulated metabolism is also observed in colorectal and pancreatic cancer cachexia models[126]. Here, tumour-derived IL-6 acts as a pivotal molecular switch between pre- and active cachectic states by impairing hepatic ketogenesis, which upon restricted caloric intake triggers a metabolic-driven cachexia that negates anti-tumour immunity[126]. Despite the functional redundancy among IL-6 family cytokines, the preponderance of evidence that IL-6 is the primary mediator of hepatic function, metabolism and immunity (**BOX 1 & BOX 2**) suggests that the pathologic actions of this family in cancer-associated cachexia may be restricted to IL-6.

In contrast to IL-6, IL-27 displays potent anti-tumour activities in the tumour microenvironment, which reflect the opposing actions described for these cytokines in autoimmune and inflammatory conditions. Studies in either *Il27p28*$^{-/-}$ or *Il27ra*$^{-/-}$ mice, or mice treated with recombinant protein show that IL-27 potentiates anti-tumour responses through effects on innate and adaptive immune cells[194]. These include IL-27-mediated control of anti-tumourigenic M1-type macrophages, the suppression of MDSCs, activation of cytotoxic $CD8^+$ T cells and the production of IFNγ and perforin by cytolytic NK cells and natural killer T (NKT) cells[194]. Collectively, this powerhouse of anti-tumour activity has set the stage for IL-27 to be developed further for potential clinical application as an anti-cancer agent.

[H1] Therapeutic strategies

Drug strategies that target IL-6 cytokine family members fall into various categories: i), blocking monoclonal antibodies that directly act on either the cytokine or the cytokine receptor; ii), recombinant cytokine regimes; iii), small molecule therapies that interfere with cytokine receptor signalling through gp130 and the JAK–STAT pathway (**FIG. 3**). While some of these modalities are in routine clinical practice, others remain in various stages of trial development. The challenge facing pharmaceutical companies is to understand the types of clinical indications that may benefit from these therapies, and to evaluate the best approach to target these inflammatory cytokines. For example, does inhibition of a cytokine, its corresponding receptor or mode of cytokine receptor signalling provide optimal therapeutic opportunities or clinical outcomes? These considerations are most pertinent considering that, as discussed previously, certain cytokine receptors (for example, IL-6Rα) bind to more than one cytokine[2,27,31,35]. Thus, therapeutic targeting of these receptor complexes may have wider consequences than inhibiting an individual cytokine. In this regard, *Il6*$^{-/-}$ and *Il6ra*$^{-/-}$ mice display phenotypic differences in wound healing, colitis severity, and control of glucose metabolism[5].

The rationale for therapeutic strategies based on blocking monoclonal antibodies is best described for IL-6[195]. These originate from studies of multiple myeloma where levels of IL-6 and sIL-6R are indicative of tumour severity, and treatment with an anti-IL-6 monoclonal antibody halted tumour expansion[196]. Although the pharmacodynamics associated with IL-6 blockade led to a worrying elevation in systemic IL-6 levels[197], the success of this intervention study nonetheless informed the design of several alternative IL-6-directed therapies. These include the anti-IL-6R blocking monoclonal antibodies tocilizumab and sarilumab, which are recommended for the treatment of inflammatory arthritis, juvenile idiopathic arthritis, adult onset Still's disease, multicentric Castleman's disease, cytokine release syndrome (including that associated with chimeric antigen receptor (CAR) T cell therapy) and giant cell arteritis[10-12,198-202]. In rheumatoid arthritis, tocilizumab and sarilumab are also prescribed as monotherapies for patients displaying an inadequate or adverse response to methotrexate[3,203].

Structure–function studies have identified amino acid motifs essential for IL-6 engagement with IL-6R and their interaction with gp130[5,204], leading to the rationale design of tocilizumab and sarilumab which target IL-6R, and sirukumab, siltuximab and clazakizumab that target IL-6 (**FIG. 3**)[5,186]. Additional biological drugs including olokizumab and EBI-031 prevent IL-6 interaction with gp130, while olamkicept (an engineered chimeric sgp130 protein that may target cytokine trans-signalling by IL-6 and IL-11)[44], NI-1201 (an anti-IL-6R monoclonal antibody), and VHH6 (junctional epitope nanobody **[G]** that recognizes the IL-6–IL-6R complex) selectively inhibit IL-6 trans-signalling[5,27,44,205-207]. These drugs show considerable promise in pre-clinical studies, early clinical trials and routine clinical practice (**FIG. 3**), although we note that the FDA has recently rejected approval of sirukumab due to safety concerns.

Another major challenge facing pharmaceutical companies is to differentiate these drugs in terms of their efficacy and safety[3,8]. For example, clinical experience with tocilizumab therapy shows that patients often develop neutropenia and adverse effects, such as increased

infections. Although therapeutic blockade of IL-6 promotes neutropaenia, tocilizumab does not promote neutrophil cell death or an increase in nonphlogistic phagocytosis by monocytic cells[208]. Instead, the development of neutropaenia may reflect the role of IL-6 in controlling granulopoiesis[209]. In this regard, the incidence and type of infections associated with tocilizumab intervention are similar to those seen with other biological drugs. Here, infections typically occur at epithelial surfaces and mucosal barriers (for example, upper and lower respiratory tract, urinary and gastrointestinal tracts) where IL-6 ensures the maintenance of immune homeostasis[3,8,210,211]. This is reflected by the incidence of adverse bacterial infections of the skin that arise in response to tocilizumab treatment of atopic dermatitis[210]. As a consequence, tocilizumab therapy appears less effective in diseases where IL-6 contributes to epithelial homeostasis or barrier integrity[5]. Thus, a prior incidence of gastric perforations or associated diverticulitis are considered contraindications for the use of tocilizumab[5,29].

In hindsight, infections on barrier surfaces may have been predicted based on the known biology of IL-6 and its predominant usage of the JAK–STAT3 pathway. For example, patients possessing inhibitory autoantibodies against IL-6 or displaying genetic mutations within the JAK–STAT signalling cassette frequently develop recurrent staphylococcal cellulitis and subcutaneous abscesses[48,49,51,212]. Indeed, patients with autosomal dominant hyper-immunoglobulin E syndrome (Job's syndrome) that is associated with STAT3 deficiency experience recurrent bacterial infections of the skin and lungs, and typically suffer from eczema[51]. These observations highlight the need to predict the involvement of IL-6 in the underlining pathology using stratification criteria that maximize patient response rates. This is epitomized for rheumatoid arthritis, where despite IL-6 or IL-6R inhibition being highly efficacious, some patients still display an inadequate response to therapy[3,7,8,203].

Other effects associated with IL-6 blocking interventions include alterations in serum lipid profiles and liver transaminases[213,214]. With respect to the former, tocilizumab leads to

augmented levels of low-density and high-density lipoprotein C, as well as changes to the composition of cholesterol[214]. Furthermore, tocilizumab suppresses levels of cholesterol-associated clinical biomarkers of cardiovascular risk, namely high-density lipoprotein-associated serum amyloid A, secretory phospholipase A2 and lipoprotein A[215]. Thus, targeting IL-6 may be of clinical benefit in treating cardiovascular conditions, including pulmonary arterial hypertension[216]. In this regard, the risk of cardiovascular events associated with tocilizumab is comparable to that seen with other agents (for example, tumour necrosis factor (TNF) inhibitors)[217]. However, tempering this notion is the recent observation that tocilizumab treatment of individuals with systemic vasculitis (Kawazaki's disease) may cause increased risk of cardiovascular complications, such as coronary-artery aneurysms[218]. In addition, serious adverse infections (such as those associated with tocilizumab and other classes of biological drug therapies) can predispose individuals to myocardial infarction or stroke[219]. Notably, systemic inflammation is also commonly associated with increased risk of cardiovascular disease[214], suggesting that biological drugs that preferentially control inflammation over lipid profiles may afford greater protection against cardiovascular events. For example, therapeutic targeting of the pro-inflammatory cytokine IL-1β with canakinumab significantly lowers the rate of recurrent cardiovascular events (myocardial infarction, stroke), but has a negligible effect on circulating lipids[220]. Therefore, biological drugs that preferentially target systemic inflammation (for example, anti-IL-1 therapy), rather than circulating lipids (for example, anti-IL-6 therapy), may provide a more effective cardio-protective intervention.

As discussed earlier, IL-6 has a major influence on the proliferation, survival and metastatic properties of cancerous cells, and studies using preclinical mouse models indicate that treatments targeting IL-6 or its receptor display therapeutic efficacy as anti-cancer agents[6]. As a consequence, several phase I/II clinical trials have evaluated the therapeutic application of tocilizumab, clazakizumab and siltuximab in prostate, lung and breast cancer, multiple

myeloma, and cancer cachexia[221-223]. While patients have shown a poor clinical response to these therapies, current trials have been restricted to non-stratified patient cohorts and highlight the need to identify predictive biomarkers for precision medicine approaches incorporating IL-6-directed therapies. Despite these poor clinical outcomes, such therapies can be exploited in cancer to counteract adverse symptoms associated with cancer immunotherapy, such as hypotension, fatigue, nausea, shivering, enhanced acute phase activity. This is particularly evident in CAR T cell therapy, where severe fever responses, hypercytokinemia and life-threatening forms of 'cytokine storm' are controlled by treatment with tocilizumab[224,225].

In addition to IL-6, the association between OSM activity and various disease states has led to the development of a humanized anti-OSM monoclonal antibody (GSK315234). However, a phase II trial designed to examine the safety, tolerability and efficacy of GSK315234 in patients with active rheumatoid arthritis showed no significant improvement in disease activity[226]. Interestingly, this lack of efficacy was attributed to an inferior binding affinity and off-rate kinetics of GSK315234 as compared to the high-affinity interaction of OSM with its receptor. Therefore, future clinical trials with high-affinity anti-OSM antibodies are anticipated not only in rheumatoid arthritis, but also in inflammatory bowel disease patients where high OSM and OSMRβ expression in intestinal tissues correlate with a lack of response to anti-TNF agents[227].

The anti-inflammatory properties of IL-6 family members in numerous *in vivo* disease models have led to the design of cytokine therapies that promote the action of CNTF, LIF, IL-11 and IL-27. For example, clinical trials have attempted to exploit the neurotrophic properties of CNTF in the treatment of degenerative diseases associated with the brain (for example, Huntington disease) and eye (for example, retinitis pigmentosa and age-related macular degeneration)[228-230]. However, adverse events including severe weight loss, hyperalgesia, coughing, muscle fatigue and pain have led to the suspension of these studies. Similarly, a trial with recombinant IL-11 in rheumatoid arthritis patients was also ineffective[231]. Nonetheless,

therapeutic strategies based on the neuroprotective properties of LIF and the anti-inflammatory characteristics of IL-27 may offer more promising applications in the treatment of multiple sclerosis, rheumatoid arthritis and other autoimmune or inflammatory diseases[155,232-234].

Several small molecule designer drugs have been developed to mimic cytokine–cytokine receptor engagement or to moderate gp130 receptor signalling (**FIG. 3**)[235-238]. For example, regulator of cartilage growth and differentiation (RCGD)-423 promotes a transient activation of gp130 dimerisation and signalling[235]. With applications in the treatment of osteoarthritis, RCGD-423 prevents chondrocyte hypertrophy and cartilage destruction in rat models of disease and promotes chondrocyte proliferation and survival[235]. Other modalities that interfere with gp130 signalling include madindoline-A, the small molecule inhibitor SC144, and the synthetic oxazolidinone derivative LMT-28[236-238]. While the clinical utility of these drugs requires further investigation, SC144 has been touted as a small molecule gp130 inhibitor for the treatment for ovarian cancer[236].

Another class of drug intervention, which is not selective for gp130 cytokine receptor signalling but has generated substantial attention over recent years, is based on blockade of the JAK–STAT3 axis[6,9]. The most advanced drugs of this type include tofacitinib, ruxolitinib, oclacitinib and baricitinib, which target JAK1, JAK2 or JAK3[239]. These JAK inhibitors are potent disease modifying agents and are approved or in clinical trials for the treatment of rheumatoid arthritis, psoriasis, myelofibrosis and other forms of autoimmune disease and cancer[239]. Similarly, various anti-sense oligonucleotide inhibitors (for example, AZD9150, which targets STAT3), modulators of inhibitory SOCS3 activity, natural chemical blockers of STAT3 activity (for example, curcumin and capsaicin) and inhibitors of STAT3 binding to DNA (for example, CPA-1, CPA-7) are also considered promising therapies for these diseases (**FIG. 3**)[240-244].

[H1] Concluding remarks

The IL-6 cytokine family is arguably the most complex group of related cytokines and affects all major biological systems within the body. In this respect, IL-6 family members are essential for development, reproduction, tissue regeneration, immune homeostasis, and defense and repair from infection, trauma or injury. However, their involvement in chronic disease and cancer identify them as diagnostic indicators, markers of disease activity, and targets of therapeutic intervention. With such widespread and often overlapping properties, the challenge remains to establish how the individual characteristics of these cytokines contribute to disease progression and the co-morbidities presented by patients with complex chronic and malignant illnesses. This is especially pertinent to drug discovery, the development of combination-type interventions, and investigations that differentiate drug action. Despite much preclinical promise, very few efficacious therapies against members of this cytokine family have reached the clinic since the approval of tocilizumab in 2009. Although small molecule interventions (for example, JAK inhibitors) offer opportunities to target intracellular components of the gp130 cytokine receptor cassette, they also act on other cytokines that use common or alternative JAK–STAT signalling mechanisms. However, an improved understanding of the molecular interactions which underpin ligand–receptor assembly and cytokine receptor signalling has seen a rapidly expanding number of next-generation agonists and antagonists for gp130 or specific family members, including IL-6, IL-11, IL-27, LIF and OSM. As we acquire new insights into the mechanisms driving local pathology, and the contribution of the immune system to mental health, and physical and psychological wellbeing, the challenge is to establish whether these agents not only decrease disease activity, but also improve the overall quality of life of patients with chronic or debilitating disease. The coming decade therefore holds considerable promise, and offers exciting opportunities to explore the therapeutic application of cytokine-directed drugs in the clinical management of autoimmune, infectious and inflammatory diseases, as well as cancers.

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Publisher's note

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Glossary terms

Janus kinase (JAK) – signal transducer and activator of transcription (STAT) pathway

A cytokine receptor signalling mechanism used by certain cytokines to sense and interpret environmental cues during inflammation and immune homeostasis.

Lymphokines

A subset of cytokines that are released by lymphocytes.

Adipokines

A subset of cytokines secreted by adipose tissue, which are sometimes called adipocytokines.

Myokines

Cytokines produced and released by myocytes in response to muscle contraction.

Pattern recognition receptors

Innate sensors that detect bacteria, viruses, fungi and other endogenous ligands generally associated with tissue damage.

Tumour microenvironment

Cellular and non-cellular compartment associated with a tumour, comprising the extracellular matrix, surrounding blood and lymphatic vessels, immune (inflammatory) cells, fibroblasts, neuroendocrine cells and adipocytes.

Cachexia

A wasting or weakening of the body due to chronic illness or cancer.

Nanobody

An engineered single-domain antibody.

Box Legends

BOX 1: Signalling mechanisms for IL-6 family cytokines and links with physiological and disease processes

Intracellular signalling mechanisms linked to the gp130 receptor system are triggered via activation of receptor-associated cytoplasmic tyrosine kinases (JAK1, JAK2 and TYK2). Activation of these proteins leads to distinct patterns of tyrosine phosphorylation and subsequent activation of the latent transcription factors signal transducer and activator of transcription 1 (STAT1), STAT3 and, to a lesser extent, STAT5. Additional signalling mechanisms associated with cytokine activation of the gp130 receptor system include processes controlled through the tyrosine-protein phosphatase SHP2. The activation of this protein promotes signalling through the RAS–RAF pathway and the SRC–YAP–Notch pathway. Activation of the RAS–RAF cascade also regulates several downstream modifiers that include the phosphorylation of MAP kinases and the AKT and mTORC1 pathways, and activities associated with the transcription factors NF-IL-6 (a C/EBP family member) and AP-1 (c-JUN and FOS). Other kinases with less defined involvements with this receptor system include SAK, HCK, FES, BTK and TEC[16]. Each of these signal transduction mechanisms control various biological processes as indicated. The heatmap depicted in the right-hand panel details how individual IL-6 cytokine family members contribute to specific physiological and immunological processes, and emphasizes their relative importance in certain disease settings (depicted below the blue line).

BOX 2: IL-6 family cytokines as regulators of metabolic processes

Members of the IL-6 cytokine family perform integral roles in health and disease, and their capacity to influence the maintenance of immune homeostasis and wellbeing can occur via regulation of various metabolic processes. The depicted heatmap summarizes the relative contribution of individual members of the IL-6 cytokine family to metabolism, and emphasizes the types of metabolic processes they affect. Certain family members, such as IL-6 and OSM, elicit these effects in various stromal tissue compartments (for example, muscle, liver, bone, brain) and inflammatory cells (for example, lymphocytes, macrophages)[246-248]. On the other hand, IL-27 displays a more restricted activity profile on select immune cell types, where it controls the expression of enzymes responsible for oxysterol generation in effector and regulatory $CD4^+$ T cells[249]. Importantly, several of these associations with metabolism have been identified through clinical observations in patients receiving biological drugs. For example, hypoferremia is a common response to systemic infection, and patients with autoimmune conditions, such as rheumatoid arthritis, frequently suffer from inflammatory anaemia[250]. Here, biological drugs against IL-6 (for example, tocilizumab) combat the development of anaemia and inhibit the hepatic-derived generation of hepcidin and haptoglobin[251,252]. These latter responses are also associated with OSM and LIF[253]. Further roles for IL-6 in metabolic processes have been identified from *Il6*$^{-/-}$ mice which develop mature onset obesity, hypertriglyceridemia and glucose intolerance, and patients on tocilizumab experience changes in serum cholesterol and triglyceride levels, along with increases in body weight[254-256]. The control of adipogenesis and lipolysis is also attributed to other IL-6 family cytokines, and these are reviewed elsewhere[257-259]. For instance, CNTF treatment in mice reduced adiposity and body weight, and improved various parameters of diabetes and hepatic steatosis, a finding that led to the development of recombinant CNTF therapy (axokine), which suppressed appetite, increased energy expenditure

and caused sustained weight loss in humans[260-262]. Consistent with a role for IL-6 family cytokines in regulating energy and glucose metabolism, acute infusion of IL-6 in mice enhanced glucose uptake and fatty acid oxidation in skeletal muscle associated with improved insulin sensitivity, and protection from diet-induced obesity[263]. Here, IL-6 released from contracting muscle drives the production of glucagon-like peptide-1 (GLP-1) within the gut and pancreas, and contributes to the maintenance of glucose homeostasis through the GLP-1 control of insulin secretion[264]. An important aspect of these metabolic-associated outcomes regulated by IL-6 family members is their link with alterations in mitochondrial activity. Here, IL-6, OSM, CT1, CNTF, and other family members influence several aspects of mitochondrial biology including changes in mitochondrial re-modelling because of cachexia, alterations in mitochondrial calcium mobilization and membrane potential, and the regulation of thermogenesis through regulation of uncoupling protein-1[265-271].

BOX 3: Cartoon depicting alternate forms of cytokine receptor signalling by the IL-6 family of cytokines

Several members of the IL-6 family adopt alternative modes of cellular activation via gp130. For example, IL-6 classical cytokine receptor signalling transduced via a gp130 homodimer is facilitated by membrane-bound forms of IL-6Rα and gp130 (for schematic purposes, only one gp130 molecule is shown). Soluble forms of the cognate non-signalling receptor-α subunits for IL-6, IL-11 and CNTF are readily detected in serum. These soluble receptors retain cytokine-binding kinetics and form receptor-ligand complexes that activate cells through binding interactions with cell-associated gp130. Cytokine binding to soluble receptors also enhances the circulating half-life of the cytokine and offers protection from proteolytic degradation[38]. These forms of cellular activation are termed cytokine trans-signalling, and provide a mechanism to

broaden the types of cells that are responsive to IL-6, IL-11 or CNTF[2]. Recent evidence has identified another form of receptor engagement termed IL-6 trans-presentation[272]. Here, IL-6 bound to membrane-bound IL-6Rα is displayed on the surface of cells (for example, specialized dendritic cells) and presented to gp130 expressed on a nearby cell type (for example, a lymphocyte) to elicit signalling via a gp130 homodimer (for schematic purposes, only one gp130 molecule is shown). These additional forms of cytokine receptor signalling contribute to the regulation of innate and adaptive immunity, and direct responses in target cells that lack specific receptors for these cytokines. Also shown are the numerous cellular processes associated with each of these signalling modes.

Figure Legends

Figure 1: Cytokine receptor usage by the IL-6 family of cytokines

(a) Members of the IL-6 cytokine family share a common ancestral link to an innate immune sensing mechanism found in *Drosophila melanogaster*. This system consists of *unpaired-3* (IL-6-like), *domeless* (gp130-like), *hopscotch* (*Drosophila* homolog of mammalian JAK) and *stat92E marelle* (*Drosophila* homolog of STAT, also referred to as *marelle*). (b, c) In mammals, all cytokines within the family activate cells through receptor complexes that contain the signal transducing receptor β subunit gp130. Three distinct forms of cytokine receptor arrangements are utilized by these cytokines. In (b), receptor complexes for IL-6 and IL-11 contain a cognate non-signalling receptor-α subunit and gp130 (termed a gp130 homodimer receptor complex), with gp130 existing as a homodimer to elicit signalling. Based on the proposed structural arrangement of the IL-6 receptor, a functioning receptor is composed of an IL-6–IL-6R–gp130 complex that is clustered into a dimer structure[16,245]. In contrast, in (c) receptor complexes for LIF, CT-1, OSM and IL-27 comprise gp130 and a second receptor subunit, which contain structural features similar to gp130 (termed a gp130 heterodimer receptor complex). These include the LIF receptor-β (LIFRβ), OSM receptor-β (OSMRβ) and IL-27Rα (also referred to as WSX-1 or TCCR). The receptor for CNTF and CLCF1 is comprised of three individual receptor subunits formed between CNTF receptor-α (CNTFR), LIFRβ and gp130. Currently, IL-31 remains the only exception to this 'gp130 rule' and the IL-31 receptor consists of IL-31Rα and OSMRβ. These alternate receptors provide cytokine specificity and couple directly to signal transduction pathways required for cellular activation (**BOX 1**).

Figure 2: The intrinsic and extrinsic properties of IL-6 family cytokines in cancer

The figure provides an overview of the cellular processes that are regulated by members of the IL-6 cytokine family, along with the predominant activation of STAT3, during tumorigenesis, tumour metastasis, and in the control of the tumour microenvironment and cancer inflammation. Cytokines with specific links to the control of these activities are shown. Note that processes associated with tumour metastasis can also contribute to the overall architecture of the tumour microenvironment and support activities linked with the development of cancer inflammation.

Figure 3: The IL-6 cytokine family as therapeutic targets

Members of the IL-6 cytokine family are drug targets for the treatment of infection, inflammation, autoimmunity and cancer. Classes of drugs include monoclonal antibodies and recombinant protein modalities for specific cytokines or cytokine receptors (shown in top target), and small molecule interventions that modulate receptor signalling activity or intracellular mechanisms linked to gp130 or JAK–STAT signalling (shown in bottom target). A cartoon depicting a representative cytokine–cytokine receptor complex of the IL-6 cytokine family is shown. Examples of these drug classes are depicted on the zoned targets. Each target is colour coded to reflect the stage of clinical development (as indicated in the key, bottom left), and the current status of an individual drug within this pipeline is represented by an annotated dot (right-hand keys). Drugs displaying related modes-of-action or common targets are accordingly coloured. Abbreviations for cytokine-cytokine receptor therapies: ciliary neurotrophic factor (CNTF), clazakizumab (CLZ), VHH6 (VHH), EBI-031 (EBI), GSK315234 (GSK), interleukin-11 (IL11), interleukin-27 (IL27), p28 subunit of interleukin-27 (p28), leukemia inhibitory factor (LIF), NI-1201 (NI), olamkicept (OLM), olokizumab (OKZ), sarilumab (SAR),

sirukumab (SIR), siltuximab (STX), tocilizumab (TCZ), vobarilizumab (VOB). Abbreviations for small molecule interventions: AZD9150 (AZD), baricitinib (BAR), capsaicin (CAP), cisplatin derivatives (CPA-1, CPA-7), CpG-*Stat3*-siRNA (CpG-*STAT3*), curcumin (CUR), dasatinib (DAS), filgotinib (FLG), LMT-28 (LMT), madindoline-A (MAD), oclacitinib (OCL), regulator of cartilage growth and differentiation-423 (RCGD), ruxolitinib (RUX), SC144 (SC), tofacitinib (TOF).